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Multiple sclerosis in the Orkney and Shetland Islands

II: The search for an exogenous aetiology

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SUMMARY In Orkney and Shetland, a survey of lifetime events was undertaken in multiple sclerosis patients and two control groups to define shared exposure to an exogenous agent or environmental insult. Analyses of demographic factors, diet, social class and occupation, housing and environment, animal exposure, schooling, travel, infectious disease, and medical history disclosed a remarkable similarity in responses between patients and controls for a majority of questions. However, differences were noted for sanitation, place of residence at onset, and animal exposure. The data give additional support for an exogenous aetiology of multiple sclerosis.

Many studies suggest that a combination of environmental and genetic factors leads to the development of multiple sclerosis (MS). Data from epidemiologic, virologic, immunologic, and genetic studies may be summarised in over-simplified form as follows:

(1) The geographic distribution of the disease is remarkable. MS occurs with increasing frequency between latitudes 40° to 60° north and south and rarely between 0° and 30°.[1 2] Occasional foci of high prevalence occur.[1]

(2) Analysis of multiple MS case households for the period during which the members lived together (common exposure) suggests that exposure to an aetiological agent occurs at about age 14.[3]

(3) Studies of migration, both from high to low and from low to high risk areas for MS, indicate that the critical age for exposure to a putative agent is about 15 years.[4 5]

(4) Serologic surveys for antibodies to common viruses have shown that MS patients have higher titres to measles and, to a lesser degree, a number of other viruses.[6 7] Radioimmunoassay of cerebrospinal fluid antibodies to measles, rubella, vaccinia, herpes simplex, and varicella-zoster viruses has demonstrated elevated antibody titres in MS patients compared with controls with other neurological diseases, a result believed to represent non-specific immune enhancement.[8]

(5) Certain antigens of the major histocompatibility complex are increased in some studies comparing MS patients with controls, although this phenomenon varies in different ethnic groups.[9 10] Futhermore, in some studies certain HLA types are associated with higher or lower antibody titres to measles and other viruses in patients, [9 11–13] and increased or decreased cell-mediated immune responses in patients.[14 15]

(6) Immunological integrity has been thought to be altered in MS patients.[16] Parodoxically, *humoral* antibody activity is enhanced to some antigens (measles and rubella) while *cellular* immune response is decreased. A diminished cellular immune response has been ascribed by Symington *et al* to the disabling effects of the disease.[15]

(7) Although increased familial occurrence is observed in MS,[3 17] investigators have not demonstrated a simple monogenic pattern of inheritance in the disease.[18] Studies of heritability in MS patients of the Orkney Islands show that the genetic contribution to the disease is small.[19]

(8) Clustering of MS patients in time and space occurred 21 years before onset and just before onset in the Orkney Islands, suggesting that two environmental factors may play a role in the aetiology of MS, representing two different environmental insults or the same insult twice before onset.[20]

PREVIOUS STUDIES OF ENVIRONMENTAL FACTORS

The geographic distribution of MS and foci of high prevalence, the demonstration of a critical age for susceptibility, evidence of clustering of patients in

time and space, and the minor role of genetic factors indicate that an exogenous agent is the predominating cause of MS. Extrapolating from that hypothesis, some investigators have undertaken careful questioning of MS patients to define shared exposure or environmental insult not found in controls.

An early study of lifetime events using controls was that of Westlund and Kurland conducted among 112 'probable' MS patients in Winnipeg, Manitoba.[21] A sample of 135 controls roughly matched to the patients for age and sex was culled from the Canadian Sickness Survey. Areas of inquiry included residential and sanitation history, occupation, travel, education, military service, animal exposure, dietary history, vaccinations and inoculations, and history of operations. The only finding to emerge ($P < 0.05$) was a greater number of operations under general anaesthesia in patients than controls before onset of MS.

The study of US Army Veterans of the second world war by Beebe and his colleagues is unique because the factors tested were derived from information obtained routinely before the disease was diagnosed.[22] Clinical records and personal data of patients with an army hospital diagnosis of MS during the second world war were reviewed. Controls were selected by screening randomly specified army serial numbers for white males who had the same year of birth and month of entry upon active duty as the patients, and who were still on active service when the index case was hospitalised for MS diagnosis. Three hundred and eighty-nine patients and matched controls were evaluated for geographic and sociologic factors and physical characteristics such as blood type. Patients differed significantly from controls for more northern location at birth and induction to military service ($P < 0.01$), urban residence at birth and induction ($P < 0.01$), socioeconomic class at induction ($P < 0.01$), and refractive errors of vision at induction ($P < 0.01$).

In Minnesota, Alter and Speer investigated a large number of possible aetiologic factors in 36 patients with MS, each with two controls from an outpatient medical clinic, matched by sex and age within three years.[23] Among 104 comparisons, 11 were significant using the authors' criterion of a P value of 0·1 or less. Surprisingly, patients showed less 'exposure' than controls in areas where differences were found. Most were upper respiratory infections before onset. In addition, a history of severe diarrhoea, polyuria, diphtheria, vaccination, severe influenza, and exposure to toxins and to cats were also more frequent among controls than patients.

The most comprehensive study, in Israel by Leibowitz and Alter, matched patients and four controls for age and sex.[4] Characteristics that differentiated patients from controls before onset were a better level of sanitation in the childhood home ($P < 0.02$) but not higher social class, residence in communities of more than 500 000 inhabitants ($P < 0.01$), older mothers ($P < 0.01$), more allergies ($P < 0.01$) and hospitalisations ($P < 0.05$) before age 15, severe injuries from age 15 until onset ($P < 0.05$), anaesthesia for labour or abortion ($P < 0.01$), smoking ($P < 0.01$), late rising ($P < 0.01$), household pets as adults ($P < 0.05$), dogs as pets before onset ($P < 0.05$), time spent outdoors in summer but not winter ($P < 0.05$), emotional trauma and stress ($P < 0.01$), and 'inhibited reactions' on a personality inventory ($P < 0.01$).

THE CURRENT STUDY

The two archipelagoes that comprise Orkney and Shetland lie in the North Sea off the coast of northern Scotland (Fig. 1). These islands possess the highest rates of MS ever reported (309/100 000 in Orkney and 184/100 000 in Shetland.[24] Orkney and Shetland are separate counties of Scotland; Orkney's population in 1974 was 17 462 and that of Shetland 18 445. There are 19 civil parishes in Orkney and 12 in Shetland. From 1974 to 1977 an extensive epidemiologic, virologic, immunologic, and genetic study was undertaken in these islands to establish the reasons for the high rates of MS and to search for factors that might shed light on the aetiology of the disease. The results of a questionnaire survey in both island groups form the basis of this paper.

Methods

The names of all patients with MS were obtained from all the general practitioners (GPs), hospital records, and MS societies in the two islands. Virtually complete ascertainment of cases was achieved because of the small size of the islands, the high level of suspicion of MS, the strong sense of community, and the length of observer residence in the islands. The criteria utilised to diagnose MS are outlined elsewhere.[25] For each patient, two controls were selected. The first control, designated a parish control, was an individual of the same sex as the patient who was born in the same year and raised in the same parish.

Because parish controls shared an environment similar to that of the patients and might be over-matched for some aetiological factor, a second control was chosen. This control, designated a discontiguous control, was born in the same year and was of the same sex but born and raised in a parish not adjacent to that of the patient. More extensive details on the selection of controls are presented elsewhere.[25]

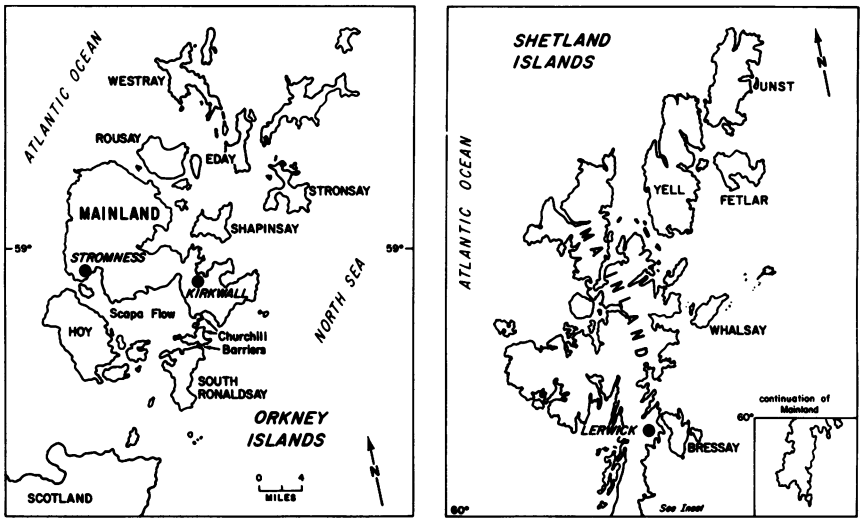

Fig. 1 *The Orkney and Shetland Islands.*

Interviews were obtained from the patient, his first-degree relatives and his spouse, the parish control, his first-degree relatives and his spouse, and the discontiguous control. The questionnaire was administered by local residents, who were trained in its use. Each interviewer had a medical background or knowledge of MS. The questionnaire was pre-tested among a small number of MS patients on the Scottish mainland and translated into the vernacular. A list of important milestones in the history of the islands was prepared for the interviewers, to facilitate memory of remote events in the respondents' lifetime: the first aeroplane landing, visits of the Royal family, and the first and second world wars.

Table 1 lists the areas of inquiry encompassed by the questionnaire. Each patient was compared with his parish and his discontiguous controls by both group and matched pair analysis. In matched pair analysis, when the patient and his control are similar in respect to a specific variable they cancel and significance is determined by the discordant pairs.[26] Only differences at the 0·05 level or higher are considered here. In most instances, analysis of data was carried out separately for each island.

Responses from available parents, siblings, and offspring of patients and parish controls were of great value in testing the internal reliability of the patients' and controls' responses to questions about place of residence, sanitary facilities and water supply at a particular residence, schools atttended, infectious diseases, diet, occupation, and travel. However, these data were necessarily incomplete, because of death of parents, emigration of some siblings, and wide variability in family size, all of which depended on the current age of the patient. Therefore, comparisons using these groups were of limited value.

The data from spouses were of less utility because of the sex and age distribution of that disease, the tendency of patients with onset at a young age not to marry, and the fact that male spouses of older patients were often deceased. There was a slight preponderance of living male spouses among the two control groups. Seventy-nine per cent of male patients and 73% of female patients were ever married; 88% of male controls and 88% of female controls were ever married. Forty-five per cent of spouses were born in the same parish as the patients; 41% of controls' spouses were born in the same parish. Data from spouses was useful, however, to tabulate the frequency of childhood events in individuals not related to the patients.

It was apparent to the interviewers and investigators that the answers to certain questions were influenced by social pressures. For example, use of alcohol was probably understated in a community where alcohol intake is reputedly high and alcoholism a major problem. History of tobacco use was also unreliable, partly as a result of the demonstration in Britain of a relationship between smoking and lung cancer shortly before the study was carried out. Information about immunisations and postnatal development was inadequate when obtained from the patient alone. Answers to the question 'If you had a dog or cat for a pet, did he sleep in or on your bed?' were believed to be unreliable because of the reluctance in this community to admit

Table 1 *Summary of questionnaire items in Orkney and Shetland Islands study of multiple sclerosis*

Item	*Significant findings**
DEMOGRAPHIC	
Marital status	No
Age of mother at birth of index	*
Month of birth of index	No
Birth order	No
Sibship size	No
Urban-rural residence	
At birth	No
At onset	*
DIET	
Potted head (pig's brain)	*
Raw eggs	No
Raw fish	No
Sea birds' eggs	No
Undercooked meat	No
Unpasteurised milk	No
SOCIAL CLASS AND OCCUPATION	
Social class by father's occupation	No
Social class by occupation of index at onset	No
Occupation of index's father by type	*
Occupation of index by type	No
HOUSING AND ENVIRONMENT	
Family density	No
Toilet facilities	No
Source of water supply	No
Piped water	No
Sewage collection	No
Use of rainwater	No
ANIMAL EXPOSURE	
Dogs	No
Cats	No
Chickens	No
Ducks	*
Geese	No
Pet birds	No
Wild birds	*
Horses	No
Cattle	No
Pigs	*
Goats	No
Sheep	No
Rabbits	*
Mice	*
Hamsters	No
SCHOOLING	
Mean years of schooling	No
Clustering by school	No
TRAVEL	
Travel outside islands	*
Mean age at first travel	*
MEDICAL AND INFECTIOUS DISEASE HISTORY	
Poliomyelitis	No
Hepatitis	No
Meningitis	No
Encephalitis	No
Tonsillectomy	No
Other operations	No
Allergies	
Nettle rash	No
Hay fever	No
Eczema	*
Other skin allergies	No
Animal allergies	No
Drug allergies	*
Any allergy	*

*Analysis in this category disclosed significant results ($P \leq 0.05$) in either Orkney or Shetland or both, between patients and parish controls or patients and discontiguous controls, or both.

a fondness for pets, despite the presence of large numbers of pet dogs and cats.

The interviews were conducted at the homes of the patients or controls. Each interviewer was responsible for arranging in advance that all available first-degree relatives were present. One to two hours were required to complete each questionnaire. Because many of the respondents had little or no experience of such surveys, the interviewers often filled out the questionnaires. When the respondent himself filled out the form, the interviewer checked each reply for completeness and ambiguity. The questionnaire was unusual in several respects. Certain pages of family information were duplicates with carbon paper inserted. The perforated duplicate copy was later removed and given to a separate interviewer specially trained to construct family pedigrees. The first two pages identified the respondent as a patient or as a healthy control or relative; the page that did not apply was removed and discarded. This feature was designed to avoid the misapprehension by normal individuals that they might have MS. A few patients have not been informed of their diagnosis and were interviewed with the restriction that they be treated as controls.

Results

Eighty-eight patients (38 males and 50 females) were living in the Orkney and Shetland Islands on prevalence day (1 December 1974), from whom 82 questionnaires were obtained. Permission to examine and question five patients was denied by their GPs and one patient refused to participate. No controls were chosen for five patients who were not born in the islands. Seventy-seven patients were available for matched pair comparisons. A total of 708 questionnaires was obtained from all participants in the study, and a breakdown by respondent category is shown in Table 2.

Table 2 *Number of respondents by category in Orkney and Shetland Islands study of multiple sclerosis*

Category	*Orkney*	*Shetland*	*Both*
Patients	49	33	82
Parish controls	45*	31	76
Discontiguous controls	46	31	77
Siblings of patients	83	72	155
Spouses of patients	32	20	52
Parents of patients	15	**	15
Offspring of patients	32	**	32
Siblings of parish controls	75	45	120
Spouses of parish controls	29	25	54
Parents of parish controls	11	**	11
Children of parish controls	34	**	34
TOTAL	451	257	708

*Because of death or emigration of all potential controls, one patient had no parish control.
**Not obtained for Shetland.

DEMOGRAPHIC

The mean age at onset of MS patients was 29·0 years in Shetland and 33·6 years in Orkney, a significant difference. Fifty-seven per cent of patients were female; a similar sex difference has been observed in most studies. The mean age at onset for all female patients was 29·9 years, and that for all male patients was 33·1 years, with a consistently higher female to male ratio up to onset at age of 40, when the ratio of males to females became higher. In the Israeli study, the female to male ratio progressively decreased with increasing age at onset.[4] No excess of MS patient births to mothers over 40 was found, in contrast to the Israeli study. However, Orkney mothers were younger at the birth of the patient than Shetland mothers (30·8 compared with 33·6, $P < 0.05$). The effect of increased maternal age on disorders in newborns is observed chiefly in those diseases for which genetic mechanisms (that is, chromosomal damage) are defined.[26 27] No evidence to support such a mechanism in MS was found in this study.

Birth order was assessed, using the method of Greenwood and Yule.[28] To be effective, the sibship must be complete as it was in this study, although the method is unaffected by sibship size. There was an insignificant tendency towards a later rank in birth order for patients as compared with controls. Variation in birth order may reflect either (1) an effect on genetic material by parental age; or (2) effects of sibship size on the home environment. As used here, birth order was an indirect method to ascertain whether contact with older siblings of school age might alter the age at exposure of the patient to childhood infections, if such infection was important in the aetiology of MS.

Sibship size was larger in Shetland patients than in Orkney patients (44% versus 33% were members of sibships of more than five individuals). The larger sibship size in Shetland patients may explain the higher maternal age at the birth of patients in Shetland.

Examination of place of residence, by town or rural area, at birth and at the onset of disease showed a marked difference in urban-rural distribution at onset for Orkney patients but not for Shetland patients (Table 3). Significantly more patients than parish controls lived at onset in a town rather than in the rural areas of Orkney.[20] However, in considering urban-rural differences in these islands, it should be kept in mind that the populations in 1971 of Kirkwall and Stromness, in Orkney, were 4617 and 2050 respectively, and that of Lerwick, in Shetland, was 6863. Furthermore, the boundaries that separate town from rural areas are poorly demarcated. One major difference between these 'urban' areas and the countryside has been the availability for most of this century of central water supply and sewage collection.

Other investigators have noted a predilection for town or urban residence in MS patients before onset. A significantly higher percentage of patients than controls in the Israeli study lived in communities of over 500 000 before onset.[4] However, no difference was observed when comparison was made between residence in communities of over and under 25 000 inhabitants. Beebe and his colleagues noted a sharp difference between MS patients and controls in size of birthplace and size of place at induction into the army; a marked preponderance of patients was born in large population centres, especially in the northern United States of America.[22]

Three studies that examined urban-rural location at or before onset of MS conflict with those cited above. A prevalence survey was conducted in north-east Scotland by Shepherd and Downie, who divided the area into 28 administrative units.[29] One rural area had the highest rate on prevalence day and by place of birth. Three adjacent wards in the city of Aberdeen had rates of MS more than 25% higher than the mean for the entire region, but the authors ascribed this difference to an excess of patients in Social Classes I and II living there. Millar found a greater risk of developing MS in the rural areas of Northern Ireland than in its largest city, Belfast.[30] In the English counties of Northumberland and Durham, Poskanzer *et al* found no urban-rural differences in prevalence rates of MS by place of birth or place of onset.[31] In most studies, factors of case

Table 3 *Urban-rural distribution of Orkney and Shetland MS patients and parish controls at birth and onset*

	ORKNEY				*SHETLAND*			
	Patients		*Parish controls*		*Patients*		*Parish controls*	
	Birth (%)	*Onset (%)*	*Birth (%)*	*Onset (%)*	*Birth (%)*	*Onset (%)*	*Birth (%)*	*Onset (%)*
Rural	76	48	76	70	81	71	81	53
Town	24	52*	24	30*	19	28	19	47

*($P<0.05$)

Table 4 *Frequency of potted head consumption in the Orkney and Shetland Islands*

Age group (years) and frequency of consumption	*ORKNEY*				*SHETLAND*			
	Patients (%)	*Controls (%)*	*Patients' siblings (%)*	*Patients' spouses (%)*	*Patients (%)*	*Controls (%)*	*Patients' siblings (%)*	*Patients' spouses (%)*
Birth to 14								
Rarely	76	75	78	72	67	56	61	60
Once a week or more	9	11	7	14	9*	5*	8	5
15 to 21								
Rarely	64	76	73	76	67	61	58	70
Once a week or more	9	6	5	10	6	3	4	0
22 and over								
Rarely	70	70	75	76	58	56	59	70
Once a week or more	4	4	4	7	3	3	5	0

*(P = 0·05), also significant by matched pair analysis.

identification probably favour urban cases even under a system of national health care.

DIET

No attempt was made to carry out a detailed survey of dietary habits among Orcadians and Shetlanders because of the obvious difficulties in obtaining adequate dietary histories over a lifetime.[21] Inquiry was limited to six unusual food items used in the islands and the frequency of consumption of these items, (never, rarely, once, twice, three, four, five, six, seven, or eight or more times a week) at ages 0–14, 15–21, and 22 and over. Questions were asked about potted head (pig's brain),* raw fish, sea birds' eggs, undercooked meat, unpasteurised milk, and raw eggs.

The only difference found in the consumption of these foods by patients and controls was for potted head, and then only for Shetland patients at ages 0–14. Seventy-six per cent of these patients, compared with 61% of both control groups combined, ate potted head at least rarely, or more often, during these ages (P = 0·05). By matched pair analysis, the difference was still significant at the 0·05 level. The frequency of consumption of potted head for patients, controls, siblings, and spouses is shown in Table 4.

There is some evidence in man that consumption of brains may be related to the subsequent development of severe neurological illness. Contamination with highly infectious brain tissue following ritualistic cannibalism of dead kinsmen is thought to be the mode of infection with the virus of kuru.[22] Creutzfeldt-Jakob disease, a presenile dementia, is 30 times more prevalent in Jews of Libyan origin than in Jews of western and central European origin in Israel.[33] Herzberg *et al.* have speculated that the custom of eating the eyeballs of sheep among Libyan Jews may give rise to the disease in these people.[34]

Westland and Kurland in Winnipeg noted a tendency towards lower consumption of butter among patients during the year before onset.[21] In a Polish study, a decrease in consumption of animal fats was noted.[35] Questions about 36 different foods and consumption of these foods before onset were asked in the Israeli study; no differences were found in consumption of fats.[4] However, patients consumed more sweet items (for example, cake).

The geographical and occupational incidence of MS was correlated with nutrition in rural Norway.[36] Butter and animal fat consumption was markedly lower in the coastal fishing districts, areas of low MS incidence, than in the farming districts where the rates of MS were higher. Although there were marked variations in rates of MS between farming districts, the authors suggested that consumption of fats may precipitate MS in susceptible persons.

Agranoff and Goldberg proposed that a geographical predisposing factor in MS may correlate with regional differences in diet and that this factor is related directly to milk production or consumption.[37] Unfortunately, these authors based their correlations upon mortality rates of MS, a notoriously unrefined method of determining the frequency of the disease.

SOCIAL CLASS AND OCCUPATION

Social class distinctions based on occupation were difficult to measure in a population where there is neither real poverty nor great wealth, and where the spectrum of occupations is small. The population is relatively well educated up to the age of 14 by requirement and very often beyond.

* No more than one or two pigs were kept by a family at any given time. When a pig was killed, all of its products would be consumed including the viscera, used in stews and soups, and the brain, which was used to make potted head. According to Mrs. Annabella Rich Annal, an 85-year-old native Orcadian, potted head is prepared as follows: The head of the animal is skinned. The eyes are removed, and the bones of the skull are broken up so that the whole skull can be fitted into a pot. The skull with brain is boiled in water with salt, pepper, onions, and the animal's feet. Head, meat, and feet with spices are boiled until the meat is easily separable from the bones. This takes three to four hours for an older animal and about one hour for a young animal. A minimum amount of water is used, just enough to keep the mixture from drying out. After the first boiling, the bones are removed from the pot, the meat is separated out and cut up finely and placed back into the pot, where the mixture is brought to a boil a second time and then placed in pots which are left to stand until their contents cool to a cheese-like consistency. Once prepared in this fashion, the potted head will keep for up to a week.

One subjective index of social class employed in this study was a question about family circumstances during childhood: 'When you were a child, did you consider your family to be very well off, well off, average, poor, or very poor?' Eighty per cent of patients and 86% of controls answered that their family was 'average'.

A more formal analysis of social class was also undertaken, using the Registrar General's classifications based on people's occupations: professional, Social Class I; intermediate, II; skilled, III; semiskilled, IV; and unskilled, V.[38] The difference in social class between patients and controls was determined by group comparisons of occupation at onset of disease. Because so few individuals had occupations at the upper and lower ends of the scale, Social Classes I and II and IV and V were combined. As shown in Table 5, little difference in social class between patients and controls was apparent in Orkney. However, in Shetland, there was an upward shift towards the higher social classes in patients (Table 6).

Higher social class in Shetland patients is explained by the greater number who reported that their occupation was crofting, which is assigned by the Registrar General to Social Class II. This result is surprising because only one-sixth of the land is suitable for cultivation. Shetlanders have traditionally engaged in more fishing than the people of Orkney, where the land is more suited to farming. However, in Shetland, a greater proportion of patients' fathers engaged in farming than did the fathers of controls (20% compared with 8%, $P < 0.05$), and it is clear that the tradition was passed on to their children. Unlike the situation in Orkney, in Shetland no increasing residence was observed in the town of Lerwick in the years previous to onset. There is little diversity of employment in the islands. Apart from farming and fishing, the occupations listed by the respondents were limited to trades, labouring, managerial positions, and public service. Because there are so few occupations, social class is not easily defined; however, to the outside observer, there is a clear social class structure. There were no occupations that posed a threat of damage from exposure to toxins.

Table 5 *Social class at onset (or assigned onset) of MS in Orkney patients and controls**

	Social class		
	I and II (%)	*III* (%)	*IV and V* (%)
Patients	12	47	41
Parish controls	17	41	41
Discontiguous controls	23	42	35

*Spouse's occupation was used for female patients who were not employed outside the home.

Table 6 *Social class at onset (or assigned onset) of MS in Shetland patients and controls**

	Social Class		
	I and II (%)	*III* (%)	*IV and V* (%)
Patients	29	50	21
Parish controls	11	44	44
Discontiguous controls	8	63	29

$x^2 = 7.09$ 2 df $P < 0.05$

*Spouse's occupation was used for female patients who were not employed outside the home.

Beebe and his colleagues devised a scale of social class for servicemen based on occupation and years of education.[22] Patients with MS had a significantly higher social class 'score' than controls. In the English counties of Northumberland and Durham, Miller *et al* demonstrated that male MS patients came from higher social classes at onset than the male population aged over 15 at risk in the two counties.[39] In Oxford, the social class of 360 patients with MS observed over a 17-year period was compared with that of two large samples of the regional population at two points in time.[40] A significant shift toward Social Classes I and II was observed for male and female patients when compared with the regional population. Kurland *et al* found that superior education characterised men with optic neuritis who later developed MS.[41] In Norway, Swank *et al* correlated the geographic distribution and incidence of MS with occupation and found the highest incidence of the disease in farming and dairy farming areas.[36] The lowest incidence of MS was found in the coastal areas where fishing was the main occupation. These were also the areas of lowest income

No social class differences between patients and controls were found in Israel, Winnipeg, or Minnesota.[4 21 23]

HOUSING AND ENVIRONMENT

Information was obtained from all respondents about sanitation for every residence in their lifetime. Matched pair analysis was carried out comparing patients and controls at birth and ages 5, 10, 15, 20, 25, and age at onset for the following indices of sanitation: family density, number of rooms in the household, toilet facilities and their location, sources of water supply and its method of delivery to the household, and drainage. No difference for any index of sanitation was noted between patients and controls at any age. However, the level of sanitation for female patients was consistently better than that for male patients (Fig. 2). In addition, as expected, there was an improvement in sanitation as the patients grew older, as shown in Table 7.

Table 7 *Matched pair data for various indices of sanitation at birth and age at onset for patients and controls in Orkney and Shetland*

		Birth		*Age at onset*		
		Indoor toilet				
		Controls			Controls	
		Yes	No		Yes	No
Patients	Yes	9	28	Yes	61	30
	No	24	77	No	17	27
		Public water				
		Controls			Controls	
		Yes	No		Yes	No
Patients	Yes	19	20	Yes	38	28
	No	19	87	No	23	28
		Piped water, including public supply				
		Controls			Controls	
		Yes	No		Yes	No
Patients	Yes	29	19	Yes	82	21
	No	19	78	No	15	20
		Public sewer				
		Controls			Controls	
		Yes	No		Yes	No
Patients	Yes	6	18	Yes	66	26
	No	17	99	No	20	23

It should be noted that in this essentially rural area centralised water supplies, even to the towns, are of relatively recent date. Although Kirkwall had a filtered water supply as early as 1911, it was not chlorinated before the second world war. Stromness had its own reservoir with filtration as early as 1906, but it still does not have a chlorinated water supply. Sewage, although collected centrally, is still discharged into the sea. The major outlet, in Kirkwall for example, is directly into Kirkwall Harbour, 100 yards offshore.

In 1963, Poskanzer *et al* described the epidemiological similarities between poliomyelitis and MS and proposed that MS might be the rare clinical manifestation of a common childhood infectious disease.[42] As with polio, where poor sanitation exists exposure to infection would occur in early life, conferring lifelong immunity. In areas of good sanitation, infection would be delayed until adolescence when the effects on the central nervous system would be more deleterious. What has come to be known as the 'sanitation hypothesis' has been supported by Leibowitz and Alter in Israel, where three indices of good sanitation in the childhood home—toilet facilities, piped drinking water, and household density of less than two persons a room—were all demonstrated to be significantly more frequent in the homes of patients than in those of controls.[4]

Westlund and Kurland found that the use of wells for drinking water within five years before onset of

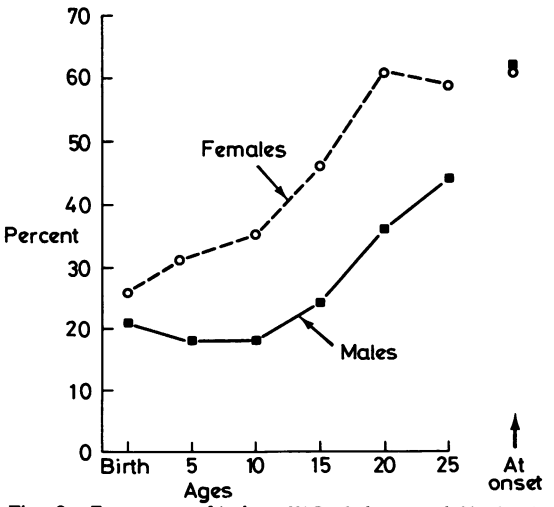

Fig. 2 *Frequency of indoor WC: Orkney and Shetland multiple sclerosis patients by age.*

MS was the same in both patients and controls, although data on other indices of sanitation were not given.[21]

EXPOSURE TO ANIMALS

Inquiry about animal and bird exposure was designed to ascertain the degree of contact, from the most intimate to the most remote, with the following: dogs, cats, chickens, ducks, geese, pet birds, wild birds, horses, cattle, pigs, goats, sheep, rabbits, mice, and hamsters. The questions concentrated on three periods in the respondents' lives: birth to age 14, 15 to 21, and 22 onwards. Matched pair analysis between patients and their parish and discontiguous controls revealed a few significant differences, all of which showed less exposure among the patients to ducks, rabbits, mice, wild birds, and pigs. The significant differences were noted only in adolescence and adulthood. In fact for all animals, there was a tendency to less exposure among patients in the adolescent and adult periods. These results most probably reflect a change in the lifestyle of the patients rather than a protective effect of exposure in the controls, and correspond to the tendency of patients to be located in the three towns in the years before onset.

In 1977, Cook and Dowling reported a significant association between ownership of small dogs and familial MS.[43] A subsequent report by the same investigators demonstrated that exposure to neurologically ill dogs in the five years before onset of MS was greater in patients than controls.[44] Demonstration of increased antibody titres to measles and canine distemper was also noted by these authors.[45] Other studies have failed to find a significant association between exposure to dogs and subsequent development of MS.[46–48] In the United States of America the annual rates were examined for canine distemper and dog bites compared with MS/control ratios by state for US white male veterans; there was no positive correlation with MS distribution.[49] Nathanson *et al* examined the distribution of MS in Iceland, where in certain regions canine distemper has been absent for more than 60 years.[50] They found that MS prevalence was as high in areas free of canine distemper as in the rest of the country. An increase in serum antibodies to canine distemper virus in MS patients has not been confirmed in other studies.[51 52]

In the present study, the sera from a small sample of patients, controls, and family members were examined for the presence of antibodies to canine distemper virus.[53] Antibody was present in 82% of all individuals; however, no significant elevations were present in any group. In the Orkney and Shetland Islands, ownership of dogs was widespread among both patients and controls. The results from group comparisons and matched pair analysis of exposure to 15 animals, including dogs, in MS patients and controls did not support any evidence of a relationship between MS and exposure to animals. However, indirect evidence of a change in the lifestyle of patients after school-leaving age emerged from the observation that patients were less exposed to animals after the age of 14.

SCHOOLING

The school-leaving age in the islands was 14. The mean number of years of schooling was comparable between patients and both control groups. Orkney patients had more years of schooling than their Shetland counterparts, because a greater number of Orkney patients attended university or schools for specialised training.

In isolated island areas such as Orkney and Shetland, it might be expected that patients and their matched parish controls would have attended the same schools for most of their childhood, with resultant common exposure to infections. However, only 50% of patients in Orkney and Shetland shared schooling with their parish controls. Because the latter were matched to patients for age, birth, and parish of birth, this result was unexpected. It is explained by the large number of primary and secondary schools in both island groups. In the 19 civil parishes in Orkney, 92 different schools were cited on questionnaires, and 60 schools were mentioned in the 12 civil parishes in Shetland.

Formal analysis of clustering of patients by school using ridit analysis,[54] failed to show significant clustering.[20]

TRAVEL

More than half of the patients and controls in Orkney and Shetland had travelled outside the islands before the age of onset of MS. More Shetland patients than Orkney patients had made one or more journeys before onset (81% compared with 58%, $P < 0.05$). For 81% of patients and 77% of controls, travel outside the islands was delayed until the age of 14, school-leaving age. The mean ages when travel was first undertaken outside Orkney were 17·8 years for patients and 19·3 for parish controls ($P < 0.01$); for discontiguous controls the mean age was 17·0. In Shetland, the comparable mean ages were 16·2 for patients, 15·8 for parish controls, and 19·9 for discontiguous controls. Among patients and controls in both islands who were born on islands other than Mainland, one patient and two discontiguous controls never left their island before onset or assigned age of onset of patient. Aberdeen, Scotland, which is about 120 miles from Orkney and 160 miles from Shetland, is the nearest large city to both islands

and it was the place most frequently visited by patients and controls. Tours of Scotland and England were also commonly undertaken.

Factors related to travel outside the islands might have been important if travel were associated with the aetiology of MS, because it was possible to ascertain when an individual left his own island or when he first travelled outside his own archipelago. However, no associations were demonstrated and no apparent leads manifested.

INFECTIOUS DISEASE HISTORY

Questions were asked about the following infectious diseases: scarlet fever, whooping cough, measles, German measles, mumps, typhoid fever, chickenpox, diphtheria, influenza, polio, hepatitis (yellow jaundice), meningitis and encephalitis. The results of serological testing for antibody titres to 17 viruses and history of common childhood infections are presented elsewhere.[53] The mean age at occurrence of the most commonly reported infections of childhood for all respondents is shown in Table 8. As might be expected in an isolated population, age at infection occurred much later than in more populous areas. From the total sample, 15 reported diphtheria, five had meningitis, and two had encephalitis. Three individuals, all of whom were patients, reported having poliomyelitis. Hepatitis was reported by 11% of all Orkney respondents and 8% of all Shetland respondents. The ratio of females to males affected was 1·8:1. Half of all the hepatitis cases reported occurred in Kirkwall, Stromness, and Lerwick, three towns with 40% of the population, which have had public water and sewage collection systems for most of this century. It was not possible to determine retrospectively whether infection was with hepatitis A or B viruses, but infection with hepatitis B virus is unlikely because blood transfusion, parenteral administration of drugs, and illicit drug use are rare in the islands.

MEDICAL HISTORY

Histories were obtained of tonsillectomy, other operations, and allergies, and there was an open-ended question about other diseases. The incidence of tonsillectomy was similar in patients (16%) and their parish controls (15%). Only five per cent of discontiguous controls had had a tonsillectomy, but the difference from patients was not significant. Poskanzer has demonstrated that MS patients had more tonsillectomies (63%) before onset of disease than their nearest sibling or spouses (about 50% in Boston).[55] The prior occurrence of tonsillectomy in eight sets of twins, in which one twin pair was concordant for MS, showed that seven of 10 affected twins had tonsillectomy before onset compared with three of eight unaffected members of twin pairs.[56] Cendrowski *et al* found no difference in rates of tonsillectomy between patients and controls in western Poland.[35]

Operations before onset of MS were no more common in patients than controls. This finding contrasts with the data from Winnipeg, where more patients than controls had operations under general anaesthesia.[21]

The paucity of operations and tonsillectomy reflects a conservative approach to medical intervention rather than a lack of medical facilities. The level of medical care in the islands is high and has been so at least since the institution of the National Health Service in Great Britain in 1948. The high ratio of GPs to patients is necessitated by the isolation of some small islands and the result is a doctor to patient ratio ranging from 1:200 to1:2000 in the towns.

All respondents were asked about allergic reactions, specifically nettle rash (hives), hay fever, eczema, other skin allergies, allergies to animals, and allergic reactions to drugs and foods. As expected, patients had more allergic reactions to drugs because a greater number of drugs were prescribed for their disease and its complications. A history of eczema was elicited from a greater number of Shetland patients than both control groups ($P < 0{\cdot}05$). No difference was found between Orkney patients and controls, who reported rates for any allergy of 65% and 59% respectively.

In several studies of allergic reactions in MS patients an increased incidence has been found in patients compared with controls.[4 56 57] Other studies

Table 8 *Mean age and frequency of occurrence for the most commonly reported infectious diseases in all respondents in the Orkney and Shetland Islands*

	ORKNEY		*SHETLAND*		
Infectious disease	*Mean age*	*Frequency (%)*	*Mean Age*	*Frequency (%)*	*
Measles	13·6	94	13·9	91	6–8
Whooping cough	8·2	78	9·3	86	3–4
Varicella	11·1	76	10·1	77	5–9
Mumps	16·3	73	17·3	73	8–10
Rubella	14·7	56	16·1	60	5–9

*Mean age of aquisition in the United States of America.

have shown a lower incidence of allergy in patients.[23 35].

A list of specific illnesses and symptoms was contained in the questionnaire, including some that might represent MS. If a respondent answered affirmatively to one of these screening questions, he or she was examined to rule out MS. One individual selected to be a control in Orkney was discovered to have MS.

Finally, patients and controls were asked to state the cause of death of their parents. A remarkable similarity between patients and controls was observed for deaths due to heart disease, cancer, and stroke, the most common causes reported.

Discussion

A striking concordance of response to more than 800 questionnaire items was noted between patients and two carefully matched control groups in the Orkney and Shetland Islands. Many of the assessed items were not independent of each other. For example, measures of sanitation such as a flushing WC or piped water or occupation and animal exposure were not mutually exclusive. Because a rigorous system of control selection was employed, the paucity of statistically significant differences serve to strengthen the validity of those positive and negative associations that were found. Although the data from this study did not disclose the aetiology of MS, some results support the hypothesis of an exogenous cause for the disease.

A difference in the level of sanitation demonstrated at various ages between female and male patients in both Orkney and Shetland is surprising. If sanitation is related to aetiology, these data suggest a possible explanation of the facts that a higher proportion of females develop MS and onset of the disease is later in males than in females. However, the possibility of finding such an aetiologic relation to sanitation in early life has been confounded by the enormous changes in sanitation that occurred in the two sets of islands after the second world war.

As in other parts of the world, there is a tendency in these islands for MS patients to live in towns. Kirkwall and Stromness comprised 20% of the population of Orkney in 1931 and 31% in 1971. In the same period the size of the two communities increased from 6500 to 7700 persons. In Shetland, Lerwick comprised 30% of the population in 1931 and 40% in 1971. In Orkney, the movement of patients to towns before onset was reflected by the data showing decreased exposure to wild and farm animals among patients compared with controls.

Some of the variations between Orkney and Shetland reflect real differences in habits between the two sets of islands. For example, fishing dominates the economy of Shetland and agriculture is secondary. The reverse is seen in Orkney. Shetlanders have larger families, which is reflected in the older age of mothers at the birth of patients in Shetland.

One particularly interesting difference between patients and controls was the tendency of MS patients in Shetland to consume potted head, which is made of animal brain.

Other analyses reflected the unusual nature of the island habitats. In particular, the common infectious diseases are acquired at much older ages than in other examined populations. These diseases do not become endemic and frequently fail to infect isolated populations. However, the later acquisition of common infections was consistent for patients and the two control groups. It is of interest that two parents of members of our study population died of measles in adult life.

As has been discussed elsewhere,[53] no evidence was found to incriminate the virus of canine distemper as the cause of MS, as manifested by extent and degree of exposure to dogs. However, dog ownership in the islands is widespread, reported in 71% of patients and controls. Canine distemper is endemic and occasionally epidemic in the dog population, and vaccination against that illness is uncommon.

The role of an environmental exposure, toxic or infectious, was confirmed in this study by the demonstration of clustering of cases in time and space.[20] In Orkney, lifetime data demonstrated temporal-spatial clustering of MS patients at two points in time: (1) at least 21 years before onset and (2) just before onset. Each cluster in time occurred on three separate islands. No clustering was seen at birth, or by chronological age or schooling. Clustering was not demonstrated in Shetland.

Previous efforts to demonstrate clustering may have failed because of lack of specificity of the data or inappropriate methodology.

These data indicate that not one but two environmental factors play a role in the aetiology of MS, representing two exposures or exposure to one environmental insult twice before onset.

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